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EFFECT OF DIETARY RESTRICTION ON TOXICOLOGY AND CARCINOGENESIS STUDIES IN F344/N RATS AND B6C3F$_1$ MICE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

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ABSTRACT

Studies were conducted to compare outcomes when four chemicals were evaluated under typical NTP bioassay conditions as well as under protocols employing dietary restriction. Specific experiments were designed to evaluate the effect of diet restriction on the sensitivity of the bioassay toward chemical-induced chronic toxicity and carcinogenicity and to evaluate the effect of weight-matched control groups on the sensitivity of the bioassays. Two chemicals, butyl benzyl phthalate and *t*-butylhydroquinone, were administered in feed; one chemical, salicylazosulfapyridine, was administered in corn oil by gavage; and one chemical, scopolamine hydrobromide trihydrate, was administered in distilled water by gavage. In each of four protocols, the effects of the chemical were assessed by a comparison between a group exposed to a single dose concentration of the study chemical and a nonexposed control group. F344/N rats and B6C3F$_1$ mice were fed NIH-07 diet either *ad libitum* or in amounts that restricted mean body weights according to the following design requirements. For the core bioassay, groups of 50 to 60 *ad libitum*-fed animals were allotted to a control group and three dosed groups for approximately 104 weeks or up to 128 weeks (*t*-butylhydroquinone study). The comparison between the control group and the group receiving the highest dose was used to represent the outcome of the bioassay under *ad libitum* feeding protocols. In a second comparison, outcomes from the group receiving the highest dose were compared with a weight-matched group of 50 to 60 untreated controls; the weight-matched controls received feed in amounts restricted so that the mean body weight matched the mean body weight of the dosed group.

Two additional groups of 48 to 60 animals (one control and one dosed group) were offered feed in amounts that limited the mean body weight of the control group to approximately 85% that of the controls fed *ad libitum* under the first protocol. Animals assigned to this dietary restriction paradigm were evaluated after 104 weeks or 130 weeks (*t*-butylhydroquinone). A fourth protocol was employed to evaluate whether an additional period of exposure (up to 1 year) would influence the neoplasm profile of animals fed a restricted diet. Two groups of approximately 50 animals (one control and one dosed group) in the butyl benzyl phthalate, salicylazosulfapyridine, and scopolamine hydrobromide trihydrate studies received restricted diets, as under the third protocol, for 3 years or until survival in either group was reduced to 20%.

Butyl benzyl phthalate caused an increased incidence of pancreatic acinar cell neoplasms in *ad libitum*-fed male rats relative to *ad libitum*-fed and weight-matched controls. This change did not occur in rats in the restricted feed protocol after 2 years; however, acinar cell adenomas were observed in three exposed, feed-restricted males at 30 months. Feed restriction is known to influence the incidence of pancreatic acinar cell neoplasms and may have prevented the full expression of this chemical-induced effect. Butyl benzyl phthalate also caused an increased incidence of urinary bladder neoplasms in female rats in the 32-month restricted feed protocol. The incidences of urinary bladder neoplasms were not significantly increased in female rats in any of the 2-year protocols, suggesting that the length of study, and not body weight, was the primary factor in the detection of this carcinogenic response.

Salicylazosulfapyridine caused an increased incidence of urinary bladder papillomas in male rats fed *ad libitum* relative to *ad libitum*-fed and weight-matched controls. This increase was associated with an increased incidence of urinary bladder calculi; the incidences of urinary bladder concretions, dilatation, and hyperplasia were also increased in dosed males. The incidences of urinary bladder papillomas and calculi were not increased in male rats receiving salicylazosulfapyridine that were fed restricted diets.

In male mice, salicylazosulfapyridine caused an increased incidence of liver neoplasms relative to the *ad libitum*-fed and weight-matched controls. This increase did not occur in the restricted feed protocols.

Liver neoplasms in mice are greatly influenced by body weight, and the marked mean body weight reduction observed in dosed male mice in the restricted feed protocols may have overridden the carcinogenic response.

Neither *t*-butylhydroquinone nor scopolamine hydrobromide trihydrate caused increased neoplasm incidences under any of the experimental protocols.

Results consistently show that feed restriction caused decreased incidences of neoplasms and nonneoplastic lesions at a variety of anatomic sites in control and dosed animals. Furthermore, the sensitivity of the bioassay to detect a carcinogenic response was altered by dietary restriction: two of the four chemicals caused increased incidences of neoplasms at three sites when evaluated under a standard *ad libitum* feeding protocol for 104 weeks. When control and dosed groups were subjected to dietary restriction, none of these three sites was detected as a target of carcinogenesis after 2 to 3 years. Rather, one different site of carcinogenesis was detected after 32 months. When dosed animals in the *ad libitum* feeding protocol were compared to weight-matched control groups, three sites were identified as targets of carcinogenesis and corresponded to the three sites discovered under the *ad libitum* feeding protocol. The magnitude of the response was greater when the weight-matched controls protocol was used. Dietary restriction of dosed and control animals decreased the sensitivity of these carcinogenesis bioassays.

Regarding the future use of dietary restriction regimens in long-term studies, only limited conclusions can be drawn because only four chemicals were evaluated and none of these proved to be a strong carcinogen. However, the results of these studies are consistent with previous findings that dietary restriction increases survival rates and decreases the incidences of neoplasms and nonneoplastic lesions at a variety of sites in rats and mice. This association between reduced body weights and decreased neoplasm incidences underlines the necessity that the doses selected for chronic studies not exceed "minimally toxic doses" so that no marked body weight reductions (or increases) will occur in the dosed groups. Such body weight changes complicate the detection of carcinogenic effects.

The following tables summarize and compare the findings from *ad libitum*-fed, weight-matched, and feed-restricted groups for each chemical.

A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 13.

Summary of the Dietary Restriction Study of Butyl Benzyl Phthalate

	Ad Libitum Feeding	Weight-Matched Controls[a]	Restricted Feed (2 Years)	Restricted Feed (Lifetime[b])
MALE RATS				
Doses	0 or 12,000 ppm in feed	0 or 12,000 ppm in feed	0 or 12,000 ppm in feed	0 or 12,000 ppm in feed
Body weights[c]	417 g, 379 g	377 g, 379 g	355 g, 336 g	363 g, 340 g
Survival rates	28/50, 22/50	34/50, 22/50	34/50, 31/50	10/50, 13/50
Nonneoplastic effects	Pancreas (acinus): hyperplasia (4/50, 12/50)	Pancreas (acinus): hyperplasia (2/50, 12/50)	None	None
Neoplastic effects	Pancreas (acinus): adenoma (3/50, 10/50)	Pancreas (acinus): adenoma (0/50, 10/50)	None	None
FEMALE RATS				
Doses	0 or 24,000 ppm in feed	0 or 24,000 ppm in feed	0 or 24,000 ppm in feed	0 or 24,000 ppm in feed
Body weights	225 g, 199 g	203 g, 199 g	187 g, 175 g	189 g, 175 g
Survival rates	25/50, 29/50	41/50, 29/50	35/50, 39/50	10/50, 11/50
Nonneoplastic effects	Urinary bladder: transitional epithelium, hyperplasia (4/50, 10/50)	Urinary bladder: transitional epithelium, hyperplasia (0/50, 10/50)	Urinary bladder: transitional epithelium, hyperplasia (0/50, 14/50)	Urinary bladder: transitional epithelium, hyperplasia (0/49, 16/50)
Neoplastic effects	None	None	None	Urinary bladder: papilloma or carcinoma (1/49, 6/50)

[a] Includes exposed group from *ad libitum* feeding protocol
[b] Survival fell to 20% at 30 months (males) or 32 months (females)
[c] Body weight data are presented as the average of weekly mean body weights for weeks 14 through 52.

Summary of the Dietary Restriction Study of *t*-Butylhydroquinone

	Ad Libitum Feeding	Weight-Matched Controls[a]	Restricted Feed (30 Months)
MALE RATS			
Doses	0 or 5,000 ppm in feed	0 or 5,000 ppm in feed	0 or 5,000 ppm in feed
Body weights[b]	425 g, 390 g	378 g, 390 g	365 g, 361 g
Survival rates	8/60, 14/60	12/60, 14/60	10/60, 22/60
Nonneoplastic effects	None	None	None
Neoplastic effects	None	None	None
FEMALE RATS			
Doses	0 or 5,000 ppm in feed	0 or 5,000 ppm in feed	0 or 5,000 ppm in feed
Body weights	232 g, 211 g	213 g, 211 g	196 g, 196 g
Survival rates	10/60, 17/60	22/60, 17/60	18/60, 24/60
Nonneoplastic effects	None	None	None
Neoplastic effects	None	None	None

[a] Includes exposed group from *ad libitum* feeding protocol
[b] Body weight data are presented as the average of weekly mean body weights for weeks 14 through 52.

Summary of the Dietary Restriction Studies of Salicylazosulfapyridine

	Ad Libitum Feeding	Weight-Matched Controls[a]	Restricted Feed (2 Years)	Restricted Feed (30 Months)
MALE RATS				
Doses	0 or 337.5 mg/kg in corn oil by gavage	0 or 337.5 mg/kg in corn oil by gavage	0 or 337.5 mg/kg in corn oil by gavage	0 or 337.5 mg/kg in corn oil by gavage
Body weights[b]	410 g, 399 g	408 g, 399 g	346 g, 330 g	348 g, 329 g
Survival rates	35/50, 23/50	31/50, 23/50	34/51, 39/50	10/49, 24/50
Nonneoplastic effects	Urinary bladder: calculus (0/50, 27/50); concretion (0/50, 10/50); dilatation (0/50, 7/50); mucosa, hyperplasia (0/50, 41/50)	Urinary bladder: calculus (0/50, 27/50); concretion (0/50, 10/50); dilatation (1/50, 7/50); mucosa, hyperplasia (0/50, 41/50)	Urinary bladder: transitional epithelium, hyperplasia (0/51, 7/50)	Urinary bladder: transitional epithelium, hyperplasia (0/49, 8/49)
	Kidney: concretion (0/50, 33/50); hydronephrosis (0/50, 28/50); mineralization (3/50, 13/50); renal tubule dilatation (0/50, 11/50); transitional epithelium, hyperplasia (10/50, 43/50)	Kidney: concretion (0/50, 33/50); hydronephrosis (0/50, 28/50); mineralization (6/50, 13/50); renal tubule dilatation (1/50, 11/50); transitional epithelium, hyperplasia (5/50, 43/50)	Kidney: concretion (0/51, 22/50); mineralization (2/51, 11/50); transitional epithelium, hyperplasia (3/51, 18/50)	Kidney: concretion (0/49, 35/50); nephropathy (39/49, 48/50); transitional epithelium, hyperplasia (1/49, 37/50)
	Spleen: hematopoietic cell proliferation (14/50, 23/50); hemosiderin pigmentation (14/50, 30/50)	Spleen: hematopoietic cell proliferation (9/50, 23/50); hemosiderin pigmentation (20/50, 30/50)	Spleen: hemosiderin pigmentation (12/51, 35/50)	Spleen: hemosiderin pigmentation (15/49, 33/49)
Neoplastic effects	Urinary bladder: papilloma (0/50, 6/50)	Urinary bladder: papilloma (0/50, 6/50)	None	None

Summary of the Dietary Restriction Studies of Salicylazosulfapyridine (continued)

	Ad Libitum Feeding	Weight-Matched Controls[a]	Restricted Feed (2 Years)	Restricted Feed (3 Years)
MALE MICE				
Doses	0 or 2,700 mg/kg in corn oil by gavage	0 or 2,700 mg/kg in corn oil by gavage	0 or 2,700 mg/kg in corn oil by gavage	0 or 2,700 mg/kg in corn oil by gavage
Body weights	45.0 g, 38.3 g	39.4 g, 38.3 g	39.2 g, 32.0 g	38.4 g, 32.2 g
Survival rates	40/50, 46/50	45/50, 46/50	42/52, 44/50	20/48, 34/50
Nonneoplastic effects	Liver: clear cell focus (2/50, 11/50); eosinophilic focus (6/50, 22/50)	Liver: clear cell focus (2/50, 11/50); eosinophilic focus (1/50, 22/50)	None	None
Neoplastic effects	Liver: hepatocellular adenoma (13/50, 42/50)	Liver: hepatocellular adenoma (8/50, 42/50)	None	None

[a] Includes dosed group from *ad libitum* feeding protocol
[b] Body weight data are presented as the average of weekly mean body weights for weeks 14 through 52.

Summary of the Dietary Restriction Study of Scopolamine Hydrobromide Trihydrate

	Ad Libitum Feeding	Weight-Matched Controls[a]	Restricted Feed (2 Years)	Restricted Feed (3 Years)
MALE MICE				
Doses	0 or 25 mg/kg in water by gavage	0 or 25 mg/kg in water by gavage	0 or 25 mg/kg in water by gavage	0 or 25 mg/kg in water by gavage
Body weights[b]	45.0 g, 36.0 g	35.9 g, 36.0 g	31.3 g, 29.1 g	31.9 g, 29.2 g
Survival rates	40/50, 39/50	41/50, 39/50	49/50, 48/50	28/50, 37/50
Nonneoplastic effects	None	None	None	None
Neoplastic effects	None	None	None	None
FEMALE MICE				
Doses	0 or 25 mg/kg in water by gavage	0 or 25 mg/kg in water by gavage	0 or 25 mg/kg in water by gavage	0 or 25 mg/kg in water by gavage
Body weights	43.2 g, 34.8 g	32.3 g, 34.8 g	29.2 g, 27.8 g	29.9 g, 27.2 g
Survival rates	33/51, 38/51	36/50, 38/51	47/50, 44/50	20/50, 19/50
Nonneoplastic effects	None	None	None	None
Neoplastic effects	None	None	None	None

[a] Includes dosed group from *ad libitum* feeding protocol
[b] Body weight data are presented as the average of weekly mean body weights for weeks 14 through 52.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on the effect of dietary restriction on toxicity and carcinogenesis studies in F344/N rats and B6C3F$_1$ mice on 20 June 1995 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 20 June 1995, the draft Technical Report on the effect of dietary restriction on toxicology and carcinogenesis studies in F344/N rats and B6C3F$_1$ mice received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. F.W. Kari, NIEHS, introduced the studies by noting that it has been recognized since the turn of the century that body weight reductions or feed restriction with concomitant decreases in body weight results in increased longevity and decreased incidences of a variety of neoplasms and nonneoplastic lesions. He showed an abbreviated list of literature reports indicating that this phenomenon is not unique to a particular species, strain, sex, tumor site, or carcinogen. Dr. Kari then reviewed the primary objectives and overall design of the studies with the four chemicals, butyl benzyl phthalate, *t*-butylhydroquinone, salicylazosulfapyridine, and scopolamine hydrobromide trihydrate, and described the four basic comparisons made in the studies. Dr. Kari provided an overview of the results, discussing discordance or disparities between the outcomes under the various protocols. Dr. Kari then discussed neoplasm sites particularly with regard to biological plausibility of weight reduction versus chemical exposure as determinants of incidence for certain neoplasms.

Dr. Goldsworthy, the principal reviewer, stated that the experimental results were predictable, given the preexisting literature and especially the limited responses seen with the four chemicals. The study corroborates earlier evidence that increased survival and decreased incidences of certain neoplasms occur in studies with dietary restriction. His major criticism was that the selected chemicals limited the number of insights and conclusions that could be made. He said that both weak and strong carcinogens should have been used and that the chosen chemicals should have targeted tissues that are sensitive to dietary restriction and that have low spontaneous neoplasm incidences, where changes due to dietary restriction in untreated animals normally could not be observed. He said this was not the case in the current studies, and it was not clear how the chemicals were chosen. Dr. Goldsworthy pointed out that the studies were properly conducted, and he thought that some of the interesting insights of the studies were obtained by examining the limited responses or subtle differences that were detected. These insights were important because there is a need both in the literature and in future studies for determining the effects of dietary restriction on very small and variable changes after long-term chemical administration.

Dr. Weindruch, a special reviewer, prefaced his comments by saying they should be viewed as those of a gerontologist with a long-term interest in the retardation of aging and diseases by dietary restriction. His main scientific concern involved the lack of a precise definition of the *ad libitum* feed intake and that the methods described did not lend confidence that the intake was precisely measured. In his experience with many strains of rats and mice, *ad libitum* feed intake varied considerably between animals. Thus, with a target of 15% mean body weight reduction, there would be a large range of individual intake values, and the use of group housing added to this problem. Dr. Weindruch spoke against the stated implication that dietary restriction "works" by preventing obesity, and he spoke for diets enriched in vitamins, minerals, and amino acids so as to balance the intakes of dietary essentials among rodents fed different levels of calories and undergoing toxicology testing. Finally, he said that the scientific rationale for the choices of the test chemicals, doses, and routes of administration needs to be stated clearly in this Technical Report.

Dr. Hart, the second special reviewer, said his foremost criticism had to do with the choice of test chemicals, commenting that if he were going to test a new paradigm for conducting bioassays, he would not randomly choose four chemicals for evaluation. Dr. Hart commented that the use of a maximum tolerated dose determined in *ad libitum*-fed animals to calculate doses in animals fed restricted diets is misleading at best, as toxic endpoints can be more severely impacted by feed restriction than by carcinogenicity. He said that using weight-restricted controls fails to take into consideration the impact that

altered caloric intake can have on a number of key physiological, metabolic, biochemical, and molecular parameters, e.g., polydipsia, increased renal clearance, or alteration of key drug metabolizing enzymes in feed-restricted animals. Dr. Hart found disconcerting a perceived lack of concern by the investigators that the data, in his view, fly in the face of 50 years of similar studies, conducted in over 20 laboratories, using over 30 different model carcinogens, which have shown that in general, dietary restriction delays the onset or reduces the severity of neoplastic changes but does not completely eliminate such changes. He felt it is also important to note that where chemically induced neoplasms appeared to be eliminated in the current studies, the mean body weights of the dosed groups were significantly less than those of the corresponding feed-restricted control groups. This compromised the assumption that the neoplasms had really been eliminated. Dr. Hart stated that his main point and, as he viewed it, the main point of this Technical Report is that if dietary restriction is used, it should be moderate. Furthermore, to enhance interstudy reproducibility, a more physiological normalizer such as adjusting dietary intake to achieve an idealized body weight curve will be needed. He proposed that a small workshop be convened to discuss and decide what an idealized body weight curve is, how to achieve it, and how to monitor it. The findings and recommendations could be reported back to the NTP Board.

Dr. Kari acknowledged the suggestions concerned with using more idealized conditions. However, he stated that the primary purpose of the dietary restriction studies was to create a data base that would help to clarify results retrospectively when there were alterations in body weight (presumably due to primary or secondary chemical effects) and to guide the interpretation of prospective studies in which alterations in body weight are expected. Thus, the experimental conditions in these dietary restriction studies needed to mimic those used in the bioassays, such as group housing and standardized diet. He said there is a definite lack of consensus in the literature as to the best experimental conditions, and it is important to have a data base that allows interpretations of effects that are often subtle. With regard to the chemicals selected for study, Dr. Kari said selection was based in part on neoplasms and nonneoplastic lesions expected to be induced by the particular chemicals selected, based on the information available at the time of selection. The chemicals in this set of studies were representative of the majority of chemicals tested by NTP; indeed, potent multisite carcinogens are exceptional.

Dr. Hart noted that the fact that the dietary restriction paradigm works under diverse conditions suggests that body weight is a factor to be considered in making an evaluation of toxicity. He thought the NTP study could serve as a good baseline; however, better model compounds are needed to test the paradigm. Dr. Weindruch said the driving force is the caloric intake *per se*. Dr. Karol stated that it is important to look at the mechanisms of effects seen in dietary restriction studies.

Dr. K. Keenan, Merck Research Laboratories, said his laboratory is already using dietary restriction; however, it is called "proper nutrition" in studies with Sprague-Dawley rats. He said the percent restriction is irrelevant, but what is important is the number of kilocalories consumed per rat per day. He showed data from studies in his laboratory and the Wistar Institute correlating kilocalories per day the with the percentages of animals bearing neoplasms and neoplasms per rat. He stated that *ad libitum* feeding is one of the most adverse events to which an animal can be subjected. Dr. Keenan concluded by summarizing the positive effects (and the lack of adverse effects) of moderate dietary restriction on animal health, longevity, and spontaneous and chemical-induced neoplasm incidences at his laboratory.

Dr. Miller stated that she supported bringing together experts in nutrition, geriatrics, and toxicology to focus on the issues around dietary restriction and toxicology studies. Dr. G.W. Lucier, NIEHS, agreed it would be a good idea for the NTP to sponsor a workshop to address these issues. The findings and recommendations could be commented on in an open meeting, perhaps through the NTP Board. Chemical selection would be an important issue. Dr. J.R. Bucher, NIEHS, commented on the increasing body weights of F344/N rats in NTP studies and the debate about whether the NTP will have to go to a more expensive and technically difficult dietary restriction regimen for all of its studies. Dr. G.N. Rao, NIEHS, said that the key to stopping or reversing the upward drift of animal body weights is to go back to the production

colonies or to establish a colony to effect controls over growth patterns. Dr. A. Turturro, NCTR, observed that breeding back will not necessarily yield the same animal. He said the large variability between individual animals within studies must somehow be controlled or reduced. Dr. W.T. Allaben, NCTR, reported that as an outcome of a conference in 1994, the FDA has put together a draft white paper looking at the issue of diet, variability of test outcomes, and the value of caloric restriction in controlling for that variability; this document will soon be presented for public comment. Dr. Kari said it is important that false negatives and false positives are not masked. Returning to the concept of a workshop, Dr. Lucier commented that the impact of dietary restriction on additional toxicologic endpoints needs to be addressed. Dr. Hart said that the term "dietary control" might be preferable to "dietary restriction." He said the FDA would cosponsor a workshop, and Dr. Karol indicated that the Society of Toxicology would be interested in serving as a cosponsor. Dr. Keenan said the Society of Toxicologic Pathologists was planning a symposium in June 1996, and he suggested that better integration among sponsoring groups was needed.